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## Exploring the use of a structural alphabet for structural prediction of protein loops.

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## Abstract

The prediction of loop conformations is one of the challenging problems of homology modeling, due to the large sequence variability associated with these parts of protein structures. In the present study, we introduce a search procedure that evolves in a structural alphabet space deduced from a hidden Markov model to simplify the structural information. It uses a Bayesian criterion to predict, from the amino acid sequence of a loop region, its corresponding word in the structural alphabet space.

Results show, that our approach ranks 30% of the target words with the best score, 50% within the 5 best scores. Interestingly, our approach is also suited to accept or not the prediction performed. This allows to rank 57% of the target words with the best score, 67% within the 5 best scores, accepting 16% of learned words and rejecting 93% of unknown words.

*Keywords : Loop conformation, conformation prediction, proteins*

# 1 Introduction

One of the most challenging problem in homology modeling remains the prediction of loops conformation. Being the less conserved regions of protein structures, they often cause serious errors in protein models because of their flexibility and the preferred occurrence of insertions and deletions. They are however known to often play an important role in protein function and stability [1]. Loop regions are organized as non repetitive conformations connecting regular secondary structures. They represent on average close to 30% of a protein. Although the conformations of these regions are, by essence, irregular, many preferred conformations have been identified [2-5]. Some authors have also suggested a relationship between loop conformation and sequence [6-7]).

Several attempts have been made to automate the prediction of the conformation of the loops. Due to the number of the possible conformations, the prediction of the conformation of loops has often been considered using conformational sampling techniques [8-11]. A possible limitation of the size of the combinatorial is to look for conformations existing in the protein structures [12-14].

Finally, with the increasing number of structures available, several attempts have been carried out to classify the loop conformations, and to extract some relationship with their associated sequences to perform prediction [15-19]. However, doing so, the authors are confronted with the problem of defining the different representative conformations used as templates, and to establish a relationship with some sequence signature.

Here, we explore whether a structural alphabet, composed of Structural Building Blocks (SBBs), learned by applying a Hidden Markov Model [20] from a collection of known structures, can be used to discretize the loop conformational space and to perform conformational prediction from loop amino-acid sequence. Previous work has shown that the distribution of SBBs differs according to loop type [21].

The advantage of using a structural alphabet is that it simplifies the structural informa-

tion, hence the combinatorial problem associated with conformational search. Also, using such representation, it is in theory possible to perform a fast search for classes of “words” that could represent the conformation of a given loop. Finally, such a representation is well suited for automated search. The aim of our work consists in (i) searching for the words of fixed size characterizing exhaustively the different three dimensional configurations of coils, and (ii) predicting these words from the sequence windows (encompassing these series of structural blocks) by a Bayesian approach using probability estimations deduced from Dirichlet functions. A criterion of predictability is introduced in the paper, it indicates the ability of discriminating the words learned (i.e. those present in the training set of coils) and the new words (i.e. the configurations newly appearing in the assessing set of coils).

## 2 Materials and methods

### 2.1 Definition of the structural alphabet

The structural alphabet used in this study was obtained by fitting a Hidden Markov Model (HMM) on a collection of proteins of known structure [20]. The structures were described as consecutive overlapping blocks of 4 residues. Each block was described by a 4-distances vector: the three distances between the non consecutive  $\alpha$ -carbons ( $d_{C_{\alpha 1}-C_{\alpha 3}}$ ,  $d_{C_{\alpha 1}-C_{\alpha 4}}$ ,  $d_{C_{\alpha 2}-C_{\alpha 4}}$ ), and the oriented distance of the last  $\alpha$ -carbon to the plane formed by the three first ones. Given such data, HMM then produces a short structural building blocks (SBBs) description of the structures. The dependence between the successive SBBs is taken into account by a first order Markov chain. The geometry associated with each block is reported Table 1. Note that SBBs are not only described by their geometry but also by their transitions with others. For example, SBBs  $\alpha_1$  and  $\alpha_2$ , describing  $\alpha$ -helices, close in terms of geometry, are distinguishable by their transitions while  $\beta_1$  and

$\beta_2$ , strongly connected, both decompose  $\beta$ -strands. The variability of each SBB is less than 1Å. Since in this study, we are interested in the loops connecting some elements of secondary structure, the distribution of each SBB in the three usual secondary structure types (helix, coil or  $\beta$ -strand) is also reported. The transition matrix associated with the Markov process is described in Camproux et al. [20].

## 2.2 Encoding of the protein structures in the structural alphabet space

Knowing both the average geometry associated with each SBB and the transition matrix associated with the first order Markov process, it is possible to translate from protein three-dimensional coordinates into the SBB space, or “alphabet space”, by using the Viterbi algorithm [22]. This algorithm directly estimates the most probable series of SBBs underlying a structure. Its advantage is that it is, in theory, much more accurate than a simple step by step procedure. Hence, the use of the transition matrix between blocks is implicitly taken into account in the present study.

## 2.3 Collection of protein structures

The encoding into the alphabet space was performed for a collection of non-redundant protein structures taken from the “culled PDB” ([http:// www.fccc.edu/ research/ labs/ dunbrack/ culledpdb.html](http://www.fccc.edu/research/labs/dunbrack/culledpdb.html)). In order to keep a balance between the largest number of proteins selected for learning and the representativity of the dataset, we have used the non redundant set presenting less than 50% sequence identity. Since loop sequences are known to be less conserved than core sequences [23], sequence identity of the loops is expected to be lower. We removed the proteins for which some ambiguity occur in the coordinates, such as missing residue or the presence of alternative conformations. This resulted in a

## 2.4 Identification of loops in the alphabet space

Given a protein description according to the structural alphabet, each loop is identified by a “structural alphabet word”. For example, for  $\alpha\alpha$  loops, we search for words of given length  $l$ , delimited on both sides by two occurrences of SBBs  $\alpha_1$  or  $\alpha_2$ . The pattern is thus:  $2\{\alpha_1, \alpha_2\} - l(X) - 2\{\alpha_1, \alpha_2\}$ , where  $l$  is the length of the loop,  $X$  any character (no series of  $\alpha_1$  or  $\alpha_2$ ) apart from  $\alpha_1$  or  $\alpha_2$  at the two first and two last locations. In this study, we have considered  $\alpha\alpha$  and  $\beta\beta$  loops using respectively  $\{\alpha_1, \alpha_2\}$  and  $\{\beta_1, \beta_2\}$  as bounds, from 3 to 13 residues long ( $3 \leq l \leq 13$ ) and their associated words. This results in a bank of structural alphabet words noted  $word_l$  describing loops of length  $l$  for  $\alpha\alpha$  loops or  $\beta\beta$  loops type. For each  $l$ -value, classes of words are defined, those differing by at least one SBB. We will label  $class_{k,l}$  a particular class of words among a collection of  $N_l$  words found in the learning set to describe a given type of loop of length  $l$ .

## 2.5 Scoring function

To predict words of length  $l$  starting from a sequence in the 20 amino-acid sequence space, we use a score based on the *a posteriori* probability calculated using Baye’s theorem:

$$p(class_{k,l}/sequence_l) = \frac{p(sequence_l/class_{k,l}) \times p(class_{k,l})}{p(sequence_l)} \quad (1)$$

where “ $sequence_l$ ” is related to a sequence of length  $l$  in the 20 amino acid description, “word” to a series of  $l$  letters in the structural alphabet space,  $class_{k,l}$  is a class of words.

$p(sequence_l)$  can be estimated according to an independence model of the  $l$  consecutive amino acids as  $\prod_i f_i$ , where  $f_i$  is the occurrence frequency of the observed amino acid  $i$  in the database. We have preferred to learn a contingency matrix specific of each type of

loop of length  $l$  on a window size of  $4 + l + 4$ . The enlargement of 4 residues both sides was done to take into account some specificity of the flanking sequences. The probabilities  $p_{i,j/l}$  of occurrence of each amino acid type  $i$  in position  $j$  of a window of size  $4 + l + 4$  are obtained as:

$$p_{i,j/l} = \frac{n_{i,j/l}}{N_l} \quad (2)$$

where  $n_{i,j/l}$  is number of occurrences of amino acid type  $i$  at location  $j$  of the window, among  $N_l$  words obtained from the database. Thus, we have:

$$p(\text{sequence}_l) = \prod_{j=1}^{4+l+4} p_{i,j/l} \quad (3)$$

Similarly, for each class  $k$ , we could estimate:

$$p(\text{sequence}_l / \text{class}_{k,l}) = \prod_{j=1}^{4+l+4} p_{i,j/k,l} \quad (4)$$

with

$$p_{i,j/k,l} = \frac{n_{i,j/k,l}}{N_{k,l}} \quad (5)$$

where  $n_{i,j/k,l}$  is the number of occurrences of amino acid  $i$  in position  $j$  of the window for the different occurrences of the class  $k$ , and  $N_{k,l}$  is the number of occurrences of the class  $k$ . Since  $N_{k,l}$  may be small, we use a different estimation of  $p_{i,j/k,l}$  based on Dirichlet functions:

$$p_{i,j/k,l} = \frac{\alpha n_{i,j/l} + n_{i,j/k,l}}{\alpha N_l + N_{k,l}} \quad (6)$$

where the coefficient  $\alpha$  conditions the estimation. Low values of  $\alpha$  lead to estimation of  $p_{i,j/k,l}$  close to values obtained for class  $k$  by (5), while large values result in values close to that obtained for the whole set of words obtained for length  $l$  with (2).



## 2.6 Criterion of acceptance of the prediction

The high variability of loops results in a possible large number of words describing loops of same length. Thus, it is possible that words not learned in the learning set, called *new* words, appear in the validation set. It is desirable to have some indicator of whether the score associated with a given word from amino-acids sequence using (1) can be related to some correct prediction. To accept or not the prediction associated with a score, we use an acceptance criterion based on the difference between the two highest scores:

$$\Delta_{1-2} = p(class_{k,l}/sequence_l)_{rank1} - p(class_{k',l}/sequence_l)_{rank2} \quad (7)$$

We accept the prediction if  $\Delta_{1-2}$  is larger than a given threshold  $T$ , i.e. when a large difference between the first and the second highest scores is observed.

## 2.7 Quantification of the results

First we distinguish the correct prediction rate ( $RCP$ ) as the fraction of words learned correctly predicted in the validation set. A correct prediction will be either to obtain the best score for the class the word belongs to (corresponding to a correct prediction at the first rank noted  $RCP(1)$ ), or to obtain the class within the 5 best scores (corresponding to a correct prediction at the fifth rank, noted  $RCP(5)$ ).

For a given length  $l$ , the validation set consists of  $N_{s,l}$  sequences tested. It can be decomposed in two parts: sequences associated with classes occurring in the learning set (“predictable classes”), denoted as  $N_{s,l,p}$ , and those associated with “new” classes, denoted as  $N_{s,l,np}$ , (“not predictable classes”). In terms of criterion of acceptance of the prediction (7), one can distinguish sequences ( $N_{s,l,a}$ ) for which the prediction is accepted and sequences ( $N_{s,l,na}$ ) for which it is not.

We define:

- the “sensitivity” associated with the threshold  $T$  as the fraction of number of predictable sequences for which the prediction is accepted ( $N_{s,l,a} \cap N_{s,l,p}$ ), among the number of predictable sequences  $N_{s,l,p}$ .
- the “specificity” associated with the threshold  $T$  as the fraction of the number of unpredictable sequences for which the prediction is not accepted ( $N_{s,l,na} \cap N_{s,l,np}$ ), among the number of non predictable sequences  $N_{s,l,np}$ .

## 3 Results

### 3.1 Loop distribution

Figure 1 shows, for different lengths, the number of words extracted from the database. Overall, 8792 words were extracted (3750 for  $\alpha\alpha$ , 5042 for  $\beta\beta$ ). Other studies found a mean loop number of 7.13 loop per protein in a comparable database (50% identity, 1411 proteins) [15,19]. Here we have a mean loop number of 7.05. Also the distribution of the loops as a function of their length is similar ( $p < 0.001$ ). We observe more  $\beta\beta$  loops, according to the observed presence of more  $\beta$ -strands in known protein structures. For length larger than 8, this is not observed.

### 3.2 Distribution of words

Figure 2 shows the distribution of the number of words and classes for different sizes. Since we have chosen a ratio of 50% of the database as learning set, we find a number of words similar in the learning and validation sets for the different length. 50% of the 8792 words appear in the learning set and 56.4% of the 5029 classes are learned in it. Only 30% of the classes correspond to short loop lengths (less than 7) with more than 67% in the learning set.

The data-bank of words appears representative only for sizes less than 7 (“short” sizes): the ratio *classes/words* remains low (38% for  $\alpha\alpha$  and 25% for  $\beta\beta$ ). Since the complexity of the conformational space increases exponentially with word size, the number of repeated words decreases when the size increases. For lengths equal to or more than 7 and less than or equal to 13 (“medium” sizes), the number of classes is close to the number of words detected (i.e. a number of occurrence close to 1 for each class). Thus, for large sizes, the database is not representative enough to obtain statistical significance of the results. However, we have kept this data since we to check the existence of some specificity inherent to the relationship SBB - amino-acid sequence.

Finally, considering the two types of loops  $\alpha\alpha$  and  $\beta\beta$ , we note that, despite the number of  $\beta\beta$  words is larger for short sizes, the number of classes identified is on the same order than for  $\alpha\alpha$  (2564 *versus* 2465). This implies a reduced variability in the alphabet space for loops  $\beta\beta$  compared to  $\alpha\alpha$  and a better representativity of the learning set. For instance, for a size of 3 and for  $\beta\beta$ , more than 90% of the overall number of classes occur in the learning set.

### 3.3 Assessment of the effectiveness of the prediction

A preliminary step has been to optimize Dirichlet weight. The optimum (in terms of correct prediction) was reached for a value of 0.1 for the  $\alpha$  parameter. The results are reported Table 2.

For this value, the self prediction score (learning set) is between 90% and 100% for all sizes. For the validation set, we first focus on the prediction of classes occurring in the learning set (occurrences of new classes of the validation set are not considered). For short words (3 to 6), for which the number of occurrences of each word is more than 1.2, the mean prediction rate based on the best rank score is of 28.4% (29.1% for  $\alpha\alpha$ , 27.8% for  $\beta\beta$ ). This was obtained for a mean number of words of 236 for each size. For medium

sizes (7 to 13) the score is of 66.6% (67.6% for  $\alpha\alpha$ , 53.7% for  $\beta\beta$ ), but with a number of predicted words between 1 to 25. Considering the 5 best scores instead of only the first one, the rates are of 50.4% for short sizes (52.8% for  $\alpha\alpha$ , 48.0% for  $\beta\beta$ ), and of 72.2% for medium sizes (83.9% for  $\alpha\alpha$ , 60.5% for  $\beta\beta$ ). These results show that the procedure has a relatively good ability to predict learned words.

Introducing occurrences of new classes, not represented in the learning set, the scores of correct prediction at the first rank are much lower: 20.9% for short sizes, and fall down to 3.7% for medium sizes. These results are simply due to the increasing complexity of loops with length and thus an increasing number of *new* classes.

### 3.4 Validation of the acceptance criterion

Since for a real prediction test, one only knows the sequence of the loop and one does not know *a priori* whether the SBB word describing it was learnt, we now analyse our results using an acceptance criterion.

The objective is here twice: (i) the identification of predictable words (learnt) and (ii) the optimization of the rate of correct prediction. For the first goal, we are interested in discarding unpredictable words, i.e to obtain a good specificity. For the latter, we prioritize the correctness of the prediction, even if this results in only a few words predicted (low sensitivity).

Table 3 gives two examples of words and associated predictions in loops of type  $\beta\beta$  for a length of 5. For instance, the class 1 corresponding to word  $\gamma_2\alpha_2\alpha'\alpha'_-\gamma_{\alpha\beta}$ , is repeated 15 times in the learning set and observed 14 times in the validation set. It is correctly predicted at the first rank in 10 upon 14 times (71.4%) and at the fifth ranks in all cases. Using criteria of acceptance ( $T = 1.28$ ), all sequences not correctly predicted at the first rank are considered as unpredictable. Class 2 corresponds to a word  $\gamma_\beta\gamma_1\alpha_2\gamma_{\alpha\beta}\gamma_\beta$ , not present in the learning set but observed 5 time in the validation set. It is always considered

as unpredictable using the criterion of acceptance.

Global results are reported in Table 4. We have considered different thresholds for  $\alpha\alpha$  loops and  $\beta\beta$  loops, and the results are presented for two sets of thresholds. First, we focus on short sizes. For the first thresholds (0.5 for  $\alpha\alpha$ , 0.64 for  $\beta\beta$ ), we have a mean sensitivity of 15.6% and a specificity of 92.9% for short words. Meaning, only a few predictable words were extracted, but almost all non predictable words have been discarded. Interestingly, among predictable words, the score of well predicted words is for the first rank only of 57.1% (compared to 28.4%), and increases up to 66.9% for the fifth best scores. For the second series (1.5 for  $\alpha\alpha$ , 1.28 for  $\beta\beta$ ), the sensitivity is lowered, but results in a better score of well predicted words (62.1%). The specificity is slightly better (97.7%). For larger values of the threshold, the sensitivity decreases, and the set of predictable words becomes not representative any longer. Hence, the weight of each failure becomes larger.

For medium words, we always obtain both a good sensitivity (53%, 48.6%) and a good specificity (91.4%, 93.8%) but due to the low number of occurrences of the words (hence a poor learning) we only predict 24.1% and 28% of good predictions.

## 4 Discussion

### 4.1 How effective is the use of a structural alphabet ?

In homology modeling, the structure of the backbone of the flanking regions as well as the sequence of the query region are assumed known. This study meets these requirements, and we have focused on two particular types of loops ( $\alpha\alpha$ ,  $\beta\beta$ ).

We perform loop conformation prediction in a structural alphabet space by accepting the equivalence between this space and the three dimensional space. By using a limited number of “characters” to reproduce at best the 3D space, we avoid part of the difficulty

inherent to using full three dimensional space, that usually leads to preliminary definition of classes of conformations. Using a discrete space is, in general, more easy than considering a continuous space, and it offers the perspective of better understanding the continuity from one conformation to another by analysing the changes in the characters. In the present study, we do not tackle the problem of going back from alphabet space to three dimensional space. We focus exclusively on our ability to predict words.

Concerning the representativity of the alphabet space, it is conditioned by the limited number of characters (SBBs) used to describe protein conformations. Here, only 10 different characters are combined to summarize loop conformations. However, we observe, for various lengths, a number of words detected very similar to number of loops reported in other studies using a three dimensional criterion [15, 19].

Finally, one main interest of using a structural alphabet is that it allows a large simplification of the combinatorial of the search, but we still not are able to reach a satisfactory representativity for each class when size increases. For short words, the number of classes remains low, for medium words, this number increases much, and the number of occurrences per class is close to 1. Thus, the goal of preserving conformational complexity seems to be reached.

## 4.2 Efficiency of the prediction procedure

In terms of prediction, we use the relationship between the structural alphabet space and the amino acid space. Different studies have shown that there exists some amino-acid sequence specificity for certain types of loops [16, 17, 19]. One major interest of the approach described herein, is to combine both the specificity of the sequence inherent to each type of loop and the specificity inherent to each class of words. Using only words, we should be confronted with the problem of the representativity of the dataset. Using Dirichlet functions, we can reach an equilibrium between the weak representativity

of words while preserving an information depending on each type of loop. A classical Bayesian procedure could not be directly applied due to a lack of representativity of certain words. Interestingly, we can study the sequence specificity associated with each word, by observing the effect of the weight used in the Dirichlet function. Here, our best results are obtained for a weight value of 0.1, which is low, and suggest that the sequence specificity of each word is important, even for long sizes, as already suggested by Efimov et al. and Martin et al. [4, 13].

How efficient can one expect the loop conformation prediction ? Our scores are difficult to compare with the results of other approaches, usually in terms of RMS deviations between the predicted conformation - i.e. one prototype of a cluster of conformations -, and the target. Using a discrete space, an adapted metrics is rather in terms of change of characters. Here, “successful prediction” consists, from the amino acid sequence, in predicting the exact word in the structural alphabet space. For small sizes (up to 7) the mean prediction of words belonging to known classes, and using the only the best score, is close to 30%. This score increases up to more than 50% if one considers the 5 best scores. Note that the value of 5 seems particularly small facing the average number of classes (118 for short loops). Lessel et al. [24] evaluated the quality of their prediction based on knowledge-base method by calculating the rms deviation to their target loops on the best 20 proposal target loops. A prediction was marked as successful, if at least one of the first three proposal had an rms deviation to the target below 1Å. Their best results are for short fragments with percentage of correct predictions of 30%, comparable to our first rank results.

Finally, we have also introduced the concept of “predictability” of a given sequence, to face the problem of unknown words. Such concept seems important since the existence of a large enough database to reach representativity for each class is far from being reached. Using such a criterion, we are able to reject as much as 93% of unknown small words.

But we accept that only 16% of known words are predicted, which is weak, among which 57% are scored at the first rank, and 67% are within the 5 best ranks. Hence, for such cases, the procedure will only propose 5 different conformations among which the correct word is present. Rufino et al. [25] made an attempt to quantify the predictability of the loops using a score based, per class, on the frequency of the amino-acids at each location. Their results showed a sensitivity larger than ours. For short words, they obtained as much as to 75% of predictable loops accepted for prediction, with a correct prediction rate of 57%. However, their specificity was only close to 50% and decreased when the correct prediction of known classes increased. We do not observe herein such a fact: the specificity of our procedure is always more than 90%.

## 5 Conclusions and perspectives

In the present study, we have investigated how plausible could be the use of a structural alphabet deduced from a Hidden Markov Model to perform conformational search for loops. Our results are still incomplete since the whole study is performed within the alphabet space, and since the conversion from such alphabet space back to the three dimensional space has not been considered. However, before considering such a step, we need first to assess whether the simplification introduced by the use of such alphabet reaches both the goal of describing loop conformational complexity and the goal of encompassing some specificity between amino-acid sequence and loop conformation.

To these regards, present results are encouraging. First, the distribution of loops observed in the structural alphabet space is comparable to that of other studies. Second, the prediction rates of the words describing loop conformations in the structural alphabet space, as well as the fact that we are able to reject the prediction for most sequences associated with words not learned, suggest strongly that our procedure is able to capture



the specificity of the sequences.

Interestingly, it is possible to extend this work towards different ways. Considering the Bayesian criterion used, results presented here were obtained by using the same sets of parameters whatever the lengths. It could be of interest to fit the Dirichlet weight and the predictability threshold for each loop type. In particular, the Dirichlet weight could be dependent on the number of occurrences and the length of each word. The rank used for correct prediction could be a function of the criterion of acceptance of the prediction. Moreover, we have not investigated the influence of the size of the amino-acid sequence window in the prediction rate.

Also, using a detailed structural alphabet to ensure a good description of the conformational complexity of the 3D structures leads to the problem of a weak representativity for classes when word size increases. We have studied the effectiveness of the procedure considering no fuzziness of the words. A further direction to improve the prediction accuracy could be to consider a “fuzzier space”, by accepting some equivalence between some of our characters defining the alphabet. One could search for the best equivalences either starting from analysing the sequence signatures associated with each SBB or starting from geometric proximity of their conformations.

Finally, it is also possible to extend the methodology to establish a direct relationship between amino-acid sequence and structural alphabet sequence without considering classes of conformation learned. The combination of such a “class independent” approach with the methodology described here could lead to significant improvements.

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## 7 Captions

### Table 1: Description of the 12 sort Structural Building Blocks (SBBs).

d1, d2, d3, d4: Mean and standard deviation of the four-distance values (see methods) for the average conformation (in Å).

rmsdw: similarity index within each SBBs, as estimated from the average root-mean-square deviation obtained on a sample of its associated segments.

%: the proportion of corresponding four-residue segments.

$\alpha$ , coil,  $\beta$ : distribution of SBBs segments on the usual secondary structures. A four-residue segment is classified in one secondary structure when its third central residue carbon, is assigned to it.

### Table 2: Prediction achieved for the learning and validation sets.

*RCP*(1): rate of correct prediction using best ranked class. (new classes not considered)

*RCP*(5): rate of correct prediction using the 5 best ranked classes. (new classes not considered)

*RCP*(1)\*: equivalent to *RCP*(1), but new classes considered (systematic bad prediction).

### Table 3: Examples of words and associated predictions using the acceptance criteria.

OLS: occurrence of class in the learning set

OVS: occurrence of class in the validation set

Criterion of acceptance:  $T = 1.28$ , (refer to methods), {1 if the sequence is considered as predictable, 0 else}.

### Table 4: Effect of the acceptance criterion

Sensitivity, specificity,  $T$ : refer to methods.

$T1$ :  $T = 0.5$  for  $\alpha\alpha$ ;  $T = 0.64$  for  $\beta\beta$ .

$T2$ :  $T = 1.5$  for  $\alpha\alpha$ ;  $T = 1.28$  for  $\beta\beta$ .

### Figure 1: Distribution of $\alpha\alpha$ and $\beta\beta$ loops according to loop size.

### Figure 2: Distribution of words and classes for $\alpha\alpha$ and $\beta\beta$ loops according to loop size.